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THE PREVENTION OF STREPTOCOCCAL UPPER RESPIRATORY INFECTIONS AND RHEUMATIC RECURRENCES IN RHEUMATIC CHILDREN BY THE PROPHYLACTIC USE OF SULFANILAMIDE

Rheumatic fever is a chronic generalized disease affecting many tissues and organs and often damaging the heart permanently. Its course in different individuals varies greatly; in some chronic valvular disease develops insidiously; in others, the so-called continuous or polycylic type, clinical or laboratory signs indicating that the rheumatic process is not quiescent, persist for months and years. In the majority of cases, however, serious cardiac damage is the result of repeated severe rheumatic attacks. Between the acute bouts these patients show no demonstrable evidence of rheumatic activity. It is in this latter type, usually described as monocylic, that prophylactic measures are most likely to prove effective.

At the present time no specfic therapy is available. Sulfonamide drugs not only fail to benefit patients with active rheumatic fever, but actually tend to increase the severity of the rheumatic symptoms, and are contraindicated even in rheumatic subjects with signs of low grade rheumatic activity. On the other hand, it was first shown by Thomas et al, and by Coburn and Moore that the administration of daily prophylactic doses of sulfanilamide to rheumatic individuals in whom the rheumatic process was inactive, prevented streptococcal pharyngitis and that patients so protected, escaped rheumatic relapses[1-2]. It was found essential to prevent infection with Group A hemolytic streptococci. Sulfanilamide given once the upper respiratory infection had developed, proved ineffective in preventing rheumatic recurrences.

These findings have been confirmed by other investigators[3-4]. None of these observers, however, had the opportunity of studying a control group living under identical conditions, where exposure to Group A hemolytic streptococci could be determined. It was thought, therefore, that the value of sulfanilamide prophylaxis could be more accurately assessed in an institution where the children were under daily medical supervision and careful bacteriological studies could be made[5].

Type of Institution. Irvington House is a sanatorium for rheumatic children ranging in age from 7 to 15 years. Each year 108 children, 66 girls and 42 boys, were selected during the summer and fall months. With few exceptions no new children were admitted from December 1 until the end of May. Rectal temperatures and pulse rates were taken three times daily. Throat cultures to determine the presence of Group A hemolytic streptococci were obtained routinely once a week on every child throughout the year. Additional throat cultures were taken on two successive days on children who developed symptoms of any kind. Antistreptolysin O titers were determined routinely every 3 to 6 weeks or more often following upper respiratory infections or during rheumatic activity.

Prophylactic Sulfanilamide. During 2 successive winters, 1940-41 and 1941-42, the patients were divided into 2 groups matched as closely as possible in regard to age, sex, number of previous rheumatic attacks and cardiac findings. Beginning in October 1940 and continuing until the following June, 54 children were given small daily doses of sulfanilamide and 54 served as controls. The same procedure was followed during the second winter, 23 children who were in the institution during 1940-41 and who remained the following year, and 31 new patients received sulfanilamide. The control group comprised 50 children. Only children who showed no clinical or laboratory evidence of rheumatic activity were given the drug. Weekly leucocyte counts and bimonthly hemoglobin determinations were done on all children receiving sulfanilamide. Samples of blood for the determination of sulfanilamide levels were taken every 3 weeks before the 8 A.M. dose of sulfanilamide.

1940-1941

Control Group. From October 1940 until February 1941, 30 of the 54 children in the control group developed streptococcal upper respiratory infections due to a single type of Group A streptococcus, type 15. After a latent period varying from 3 to 21 days, 14 of these 30 patients developed definite rheumatic manifestations and 4 additional children laboratory evidence of rheumatic activity. Two children in the control group became "contact" carriers of type 15 streptococcus without developing symptoms of any kind.

Sulfanilamide Group. Only one child receiving sulfanilamide as a prophylactic contracted pharyngitis due to type 15 streptococcus. No rheumatic sequalae developed. Ten children in this group became "contact" carriers of the epidemic inducing strain.

1941-1942

The results were similar to those obtained the previous winter.

Control Group. An outbreak of upper respiratory infections due to a single type of Group A streptococci, provisional type 36, occurred. From October 1941 until February 1942, 18 of 50 children, who were not receiving sulfanilamide, contracted pharyngitis due to this type. Following a latent period varying from 10 to 18 days, 10 of these 18 children developed rheumatic sequelae.

Sulfanilamide Group. Again only one child receiving sulfanilamide contracted pharyngitis due to the epidemic strain of streptococcus. Following a latent period this boy developed mild rheumatic manifestations lasting 10 days.

Four children in this group became "contact" carriers of provisional type 36 streptococcus.

Summary. During both years the contrast in the incidence of streptococcal upper respiratory infections and rheumatic relapses in the treated and untreated groups was striking. Only 2 of 108 children receiving sulfanilamide contracted streptococcal pharyngitis and only one of these developed rheumatic manifestations. Among the 104 children serving as controls 48 contracted streptococcal pharyngitis and 23 of these 48 or nearly half, developed definite rheumatic relapses and 5 additional children had laboratory evidence or mild clinical symptoms suggesting rheumatic activity. No rheumatic recurrences were observed in children who escaped streptoccal upper respiratory infections.

Dosage. During 1940-41 an average blood level of 2 mgm. % was maintained. In most instances children weighing 75 lbs. or less were given 1 gram of sulfanilamide daily in 3 divided doses and children weighing more than 75 lbs. 1.3 to 2 grams. During 1941-1942 the dosage was decreased slightly so as to maintain an average blood level of 1.5 mgm. %.

During each year one child developed streptococcal pharyngitis in spite of sulfanilamide prophylaxis. In one instance infection occurred in a patient with a blood level of 2 mgm. %. This girl may have been particularly susceptible to the epidemic inducing strain of streptococcus or the infecting dose may have been unusually large. In the case of the other child the blood level at the time of infection was 0.95 mgm. %. In our opinion a concentration of 1 mgm. % is probably too low to be effective.

Toxic reactions. The incidence of toxic manifestations in our series was high, 15%, but no serious reactions were encountered. The following symptoms were observed: fever, abdominal pain, nausea, erythema and urticaria. A gradually developing leucopenia accompanied by a fall in polymorphonuclear leucocytes was encountered in 3 children. The blood picture returned to normal within a few days when the drug was discontinued.

The possibility that agranulocytosis may develop in patients receiving prophylactic sulfanilamide must always be borne in mind and constitutes the greatest hazard of this form of treatment[6].

General Condition of Children Receiving Prophylactic Sulfanilamide. The children who did not develop toxic reactions within 5 weeks tolerated the drug well. There were no subjective complaints. In most instances the patients continued to gain weight at the same rate as before medication was started. The hemoglobin of most children receiving sulfanilamide tended to fall slightly and remained at a level somewhat lower than normal throughout the course of the treatment. The hemoglobin rose to its previous level when the drug was discontinued.

Administration of Sulfanilamide During 2 Successive Winters. Twenty-three patients who received sulfanilamide during both winters showed no evidence of sensitization when the drug was restarted after a lapse of 5 months.

Conclusions. In considering any prophylactic measure the danger inherent in the treatment must be weighed against the seriousness of the disease. Many observers are of the opinion that the severity of rheumatic fever in this country is declining. In any given child, however mild the first rheumatic manifestations may be, it is impossible to predict the subsequent course of the disease. The ultimate value of sulfanilamide prophylaxis can be determined by protecting rheumatic individuals from streptococcal upper respiratory infections not for 1 or 2 years but for at least 5 years. To date no reports on the prophylactic value of some of the less toxic sulfonamide drugs such as sulfadiazine have been published. It seems probable, however, that less toxic compounds as effective as sulfanilamide in preventing rheumatic relapses will be developed. In the meantime the sulfanilamide studies have added further evidence that infection with Group A hemolytic streptococci plays an important role in the etiology of rheumatic fever.

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REFERENCES

1. Thomas, C. B., France, R., and Reichsman, F., J.A.M.A., 1941, 116, 551.
2. Coburn, A. F., and Moore, L. V., J. Clin. Invest., 1939, 18, 147.
3. Hansen, A. E., Platou, R. V., and Dwan, P. F., Am. J. Dis. Child., 1942, 64, 963.
4. Chandler, C. A., and Taussig, H. B., Bull Johns Hopkins Hosp., 1943, 72, 42.
5. Kuttner, A. G., and Reyersbach, G., J. Clin. Invest., 1943, 22, 77.
6. Stowell, D. D., and Button, W. H., Jr., J.A.M.A., 1941, 117, 2164.